Anemias in Children

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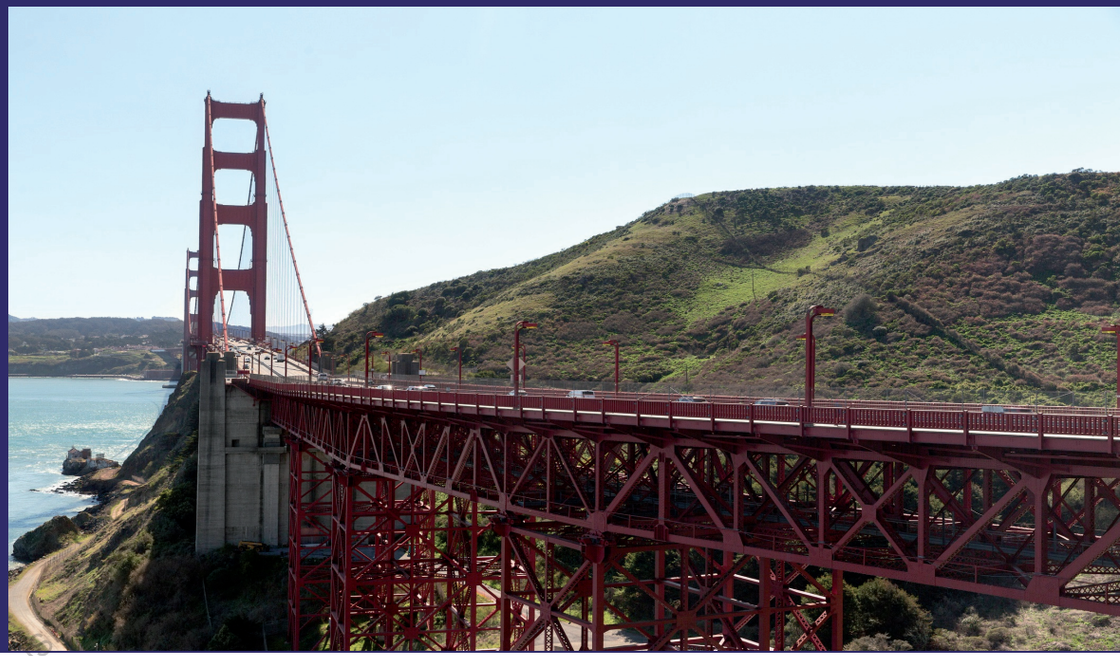
This book discusses anemia which is a common problem in children. About 20% of children in the U.S. will be diagnosed with anemia at some point. A child who has anemia does not have enough red blood cells or hemoglobin. Hemoglobin is a type of protein that allows red blood cells to carry oxygen to other cells in the body. Most common causes of pediatrics anemias were mentioned.
Pediatric anemia refers to a hemoglobin or hematocrit level lower than the age-adjusted reference range for healthy children. Physiologically, anemia is a condition in which reduced hematocrit or hemoglobin levels lead to diminished oxygen-carrying capacity that does not optimally meet the metabolic demands of the body.
Anemia is not a specific disease entity but is a condition caused by various underlying pathologic processes. It may be acute
or chronic.
Diagnostic and therapeutic methods also were discussed in this informative book.



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List of content:

Dedication:

To our parents

Acknowledgement:

We are grateful to everyone whom support us during our educational and professional life , our teachers , friends and colleagues and we hope that book assist our student to know more about different types of pediatrics anemia's.

Background

Anemia is defined as a hemoglobin level of less than the 5th percentile for age. Causes vary by age. Most children with anemia are asymptomatic, and the condition is detected on screening laboratory evaluation. Screening is recommended only for high-risk children. Anemia is classified as microcytic, normocytic, or macrocytic, based on the mean corpuscular volume. Mild microcytic anemia may be treated presumptively with oral iron therapy in children six to 36 months of age who have risk factors for iron deficiency anemia. If the anemia is severe or is unresponsive to iron therapy, the patient should be evaluated for gastrointestinal blood loss. Other tests used in the evaluation of microcytic anemia include serum iron studies, lead levels, and hemoglobin electrophoresis. Normocytic anemia may be caused by chronic disease, hemolysis, or bone marrow disorders. Workup of normocytic anemia is based on bone marrow function as determined by the reticulocyte count. If the reticulocyte count is elevated, the patient should be evaluated for blood loss or hemolysis. A low reticulocyte count suggests aplasia or a bone marrow disorder. Common tests used in the evaluation of macrocytic anemias include vitamin B_{12} and folate levels, and thyroid function testing. A peripheral smear can provide additional information in patients with anemia of any morphology [1].

Globally, anaemia affects 1.62 billion people (95% CI: 1.50–1.74 billion), which corresponds to 24.8% of the population (95% CI: 22.9–26.7%). The highest prevalence is in preschool-age children (47.4%, 95% CI: 45.7–49.1), and the lowest prevalence is in men (12.7%, 95% CI: 8.6–16.9%). However, the population group with the greatest number of individuals affected is non-pregnant women (468.4 million, 95% CI: 446.2–490.6) [2]. Anemia impairs normal development in children and it constitutes a major public health problem in young children in the developing world with wide social and economic implications. Thus, decreased physical exercise tolerance and intellectual performance have been associated with mild anemia, which may lead to a slowdown of growth in children. In sub-Saharan Africa in children less than five years of age, the prevalence of anemia varies from 43% in Zaire to 74% in Tanzania. Its etiology in tropical countries is multifactorial: thus, the most important risk factors need to be identified for prevention strategy. Anemia is commonly associated with nutritional deficiencies such as iron deficiency, the main factor responsible for microcytic anemia, while folate or vitamin B_{12} deficiencies are responsible for macrocytic anemia. Similarly, parasitic diseases such as malaria and ankylostomiasis have been reported to lead to a high prevalence of anemia during childhood.3–6 Sickle cell disease has been also recognized as an important risk factor for anemia in sub-Saharan countries. However, the relative contributions of these etiologies remain unclear. We conducted a prospective study in southern Cameroon to analyze the epidemiology of anemia and to specify the role of malaria, compared with others risk factors, in the development of anemia in 206 children less than five years of age [3].

Epidemiology

Approximately one-third of the world's population (32.9%) was estimated to suffer from anemia in 2010.The population groups most vulnerable to anemia include children under 5 years of age (42% with anemia in 2016), particularly infants and children under 2 years of age; WRA (39% with anemia in 2016); and pregnant women (46% with anemia in 2016). Females were consistently at greater risk of anemia than men across almost all geographic regions and in most age groups. Other at-risk groups include the elderly, as the prevalence of anemia among adults over 50 years of age rises with advancing age.

The prevalence of anemia also varies by geographic region. Sub-Saharan Africa, South Asia, the Caribbean, and Oceania had the highest anemia prevalence across all age groups and both sexes in 2010. At the country level, anemia among WRA and children under 5 years of age is a moderate-to-severe public health problem (20% or greater as defined by WHO) in the majority of WHO member states. Progress on decreasing anemia has been overall slow and uneven. For all age groups and both sexes, anemia is estimated to have decreased roughly seven percentage points between 1990 and 2016, from 40% to 33%. The WHO Global Nutrition Target 2025 on anemia aims to reduce anemia in WRA by 50% by 2025. Based on a global prevalence of 29–38% anemia among WRA (nonpregnant and pregnant, respectively) as of 2011, a reduction of 1.8–2.4 percentage points per year would be required to meet this target [4].

Hematopoiesis

The formation of blood cells (hemopoiesis) is determined by the interaction of multiple genes and involves cytokines and other protein factors. The relative ease with which hematopoietic cells can be studied and the development of new techniques in cell biology have enabled us to understand many of the factors determining cell renewal and differentiation. Based on this knowledge, major progress has been made in the last 15 yr in the treatment and diagnosis of many hematological disorders. In this chapter, we describe the cell types involved in normal hematopoiesis and their interactions with one another. Furthermore, the basic techniques necessary for the study of hematopoietic cells in the normal and pathological state are outlined.

During the first few weeks of embryonic life, the formation of blood cells takes place in the yolk sac. Later, until the sixth or seventh month of fetal development, the liver and spleen are the major hematopoietic organs. By the time of birth, more than 90% of all new blood cells are formed in the bone marrow. Here, the progenitor cells are found, in various stages of development, situated in anatomical niches in the bone marrow from where they are then released into the marrow sinuses, the marrow circulation, and further on into the systemic circulation.

During infancy and childhood, the marrow of all bones contributes to hematopoiesis. During adult life, hematopoietic marrow is restricted to certain bones (e.g., pelvic bones, vertebral column, proximal ends of the femur, skull, ribs, and sternum). Even in these areas, a proportion of the marrow cavity consists of fat. During periods of hematopoietic stress (e.g., in severe hemolytic anemias and in some myeloproliferative disorders), the fatty marrow as well as the spleen and liver can resume the production of blood cells. This situation is called extramedullary hematopoiesis.

Growth and differentiation of hematopoietic cells in the bone marrow is regulated by the extracellular matrix and microenvironment provided by stromal cells. These cells, including macrophages, fibroblasts in various stages of differentiation, endothelial cells, fat cells, and reticulum cells, nurture hematopoietic stem cells and progenitor cells by producing growth factors like granulocyte/ macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), interleukin (IL)-6, or stem cell factor. Other cytokines secreted by stromal cells regulate the adhesion molecules present on hematopoietic cells, allowing them to remain in the bone marrow or migrate to an area where the respective cell type is needed.

All hematopoietic cells of the organism derive from pluripotent stem cells that are capable of both self-renewal and differentiation into all hematopoietic lineages. Stem cell provides progenitor cells for myelo- and monopoiesis, erythropoiesis, megakaryopoiesis, and lymphopoiesis. Other cell types such as stromal cells or dendritic cells also derive from the pluripotent hematopoietic stem cell. It has been estimated that one stem cell gives rise to at least

10^6 mature hematopoietic cells. Under normal conditions, the stem cells provide hematopoietic cells for the entire life span. Each day, a healthy adult organism produces more than 10^{12} hematopoietic cells. Many blood disorders.

Stem cells are very rare, representing less than 0.01% of all nucleated cells in the normal bone marrow. Based on animal experiments, the morphology of stem cells is thought to be similar to that of small lymphoid cells. In recent years, the marker expression of human stem cells has been studied. Human stem cells express the surface proteins CD34 and c-kit and are negative for CD38 and lineage-specific markers. In animal systems, stem cells can be assayed as spleen colony-forming units (CFU) in irradiated hosts. Only the more differentiated progenitors of human hematopoietic cells can be tested for their ability to form colonies in soft agar or methylcellulose. One of the earliest progenitor cells in such systems is CFU_{GEMM}, which contains granulocytes, monocytes, erythroid cells, and platelet progenitors. From this pluripotent progenitor, more specialized progenitors are formed. Under normal conditions, the majority of stem cells is dormant (G0 phase of the cell cycle). A stem cell divides only to maintain the steady state of hematopoiesis or to meet the body's demand for progenitor cells (stochastic model of hematopoiesis). The daughter cells then either differentiate into determined progenitor cells (e.g., lymphohematopoietic cells) or return to dormancy by reentering the stem cell pool. Stem cells can be enriched and transplanted (stem cell or bone marrow transplantation). The stem cell donor does not experience a detectable loss of stem cells.

There are several hierarchical levels of stem and progenitor cells. In general, the hematopoietic growth factors do not act on true stem cells, but support the survival and the differentiation of committed cells. Although "early-acting" cytokines such as stem cell factor, FLT3-ligand, G-CSF, or IL-6 regulate the earliest progenitor cells, "late-acting" cytokines such as erythropoietin for erythropoiesis or thrombopoietin for megakaryopoiesis support the growth and differentiation of progenitor cells that are already committed to their respective lineage. Many other cytokines play a positive or negative role in the differentiation of hematopoietic cells.

The gene expression in early stem cells is complex and involves the co-expression of multiple transcription factors. For example, the combination of C/EBP D and Pu 1 directs the expression of the receptor for G-CSF, which is critical for early myelopoiesis. Pu 1 binds to and regulates the promotors of several myeloid growth-factor receptor genes. The Notch family of transmembrane receptors was described in Drosophila as a ligand-dependent suppressor of cell differentiation. Similar receptors have recently been found on human stem cells, suggesting that they may also be involved in maintaining an undifferentiated state. The significance of telomeres present in human stem cells and the activity of telomerase in these cells is currently of interest. Telomeres are specialized structures at the end of chromosomes that change with cell division. Shortening of telomeres is associated with cellular aging. Telomerase is an enzyme capable of extending the length of telomeres. It has now been found that adult stem cells have shorter telomeres than fetal stem cells and that the length of telomeres shortens further after transplantation. The activity of telomerase is generally low in stem cells (which corresponds to

their quiescent state), but can be upregulated on entry into the cell cycle. The implications of these findings are not yet clear, but they may indicate that not all stem cells are immortal.

ERYTHROPOIESIS:

Red blood cells are specialized cells that deliver oxygen to tissues and remove carbon dioxide from the human body. Erythropoiesis, the "making of red cells," involves many different genes and gene products that lead to the production of the mature cell. Erythropoiesis begins at the level of the multipotent stem cell, which then undergoes commitment and differentiation. Listed as follows are the stages of erythroid differentiation:

1. Stem cell.
2. BFU-E (burst-forming unit, erythroid; immature erythroid progenitor).
3. CFU-E (colony-forming unit, erythroid; more mature erythroid progenitor).
4. Proerythroblasts, erythroblasts, normoblasts (morphologically recognizable red cell precursors, they still have a nucleus, multiply by cell division, and progressively decrease in size as hemoglobin content increases).
5. Reticulocytes; mature red blood cells (erythrocyte).
   Remnants of ribosomal RNA can be visualized in reticulocytes; no nucleus is present in the mature red cell. The vast majority of nucleated red-cell precursors are confined to the bone marrow.
   One proerythroblast gives rise to 12–16 mature red blood cells within 5–10 d.
   One proerythroblast gives rise to 12–16 mature red blood cells within 5–10 d. The erythropoietic differentiation is modulated by several cytokines (stem cell factor, IL-3, GM-CSF, and erythropoietin). Erythropoietin is the major cytokine that adapts the production of red cells to the needs of the organism. Both the proliferation and differentiation of CFU-E and late BFU-E are accelerated as a response to erythropoietin. In response to low hemoglobin levels in the blood and tissue hypoxia, the production of erythropoietin by the kidneys is increased. When the serum levels of erythropoietin are increased, both the rate and the speed of erythropoiesis increase. Erythropoietin binds to specific receptors on red cell precursors, consequently activating the Janus 2 kinase (JAK2) by tyrosine phosphorylation. This in turn activates the STAT pathway and Ras signal transduction. A number of transcription factors are involved in the activation of erythroid-specific genes including GATA1, GATA2, NFE2, SCL, EKLF, and myb. During early erythropoiesis, the downregulation of the SCL gene precedes the downregulation of the GATA 2 and GATA 1 genes. In bone marrow, erythropoiesis occurs in distinct anatomic locations called erythroblastic islands, in which a central macrophage is surrounded by a ring of developing erythroblasts. Important mediators of the cell–cell contact in the erythroid islands include the integrins, the immunoglobulin (Ig) superfamily, and cadherins. In states of chronic tissue hypoxia (e.g., in hemolytic anemias) the proportion of the marrow devoted to erythropoiesis expands and sometimes transforms a large portion of the fatty marrow into active hematopoietic marrow.

Hemoglobin**:**

Hemoglobin is the molecule responsible for the transport of oxygen. Under physiological conditions, three types of hemoglobins exist:

- Hemoglobin A (D2E2): major adult hemoglobin (96–98%).
- Hemoglobin F (D2J2): predominant during fetal development, 60–80% at birth, 0.5–0.8% during adult life.
- Hemoglobin A2 (D2G2): normally 1.5–3%.

  The hemoglobin molecule has a molecular weight of 64,500 and consists of four polypeptide chains, each carrying a heme group. The heme synthesis starts with the amino acid glycine. Later, porphobilinogen, uroporphyrinogen, coproporphyrinogen, and protoporphyrin are formed as intermediate steps. Iron (Fe^{2+}) is supplied from serum transferrin and combines with protoporphyrin to form heme. One heme molecule then binds with one globin chain to form the hemoglobin molecule that avidly binds oxygen.

  The release of oxygen from red cells into tissue is strictly regulated. Under normal conditions, arterial blood enters tissues with an oxygen tension of 90 mmHg and hemoglobin saturation close to 97%. Venous blood returning from tissues is deoxygenated. The oxygen tension is about 40 mmHg, the hemoglobin saturation is 70–80%. The oxyhemoglobin dissociation curve describes the relation between the oxygen saturation or content of hemoglobin and the oxygen tension at equilibrium.

  The affinity of hemoglobin for oxygen and the deoxygenation in tissues is influenced by temperature, by CO2 concentration, and by the level of 2, 3-diphosphoglycerate in the red cells. In the case of tissue or systemic acidosis, the oxygen dissociation curve is shifted to the right and more oxygen is released. The same effect results from the uptake of carbon dioxide, which raises the oxygen tension of carbon dioxide. This facilitates the unloading of oxygen. As the body temperature increases, the affinity of hemoglobin for oxygen decreases, thereby facilitating oxygen release.

  The oxygen supply to peripheral tissues is influenced by three mechanisms:

  1. The blood flow, which is controlled by the heart beat volume and the constriction or dilatation of peripheral vessels.
  2. The oxygen transport capacity, which depends on the number of red blood cells and the hemoglobin concentration.
  3. The oxygen affinity of hemoglobin.

  In anemic patients, the stroke volume of the heart is increased, the heart beats faster (tachycardia), and, in addition, the 2,3-diphosphoglycerate concentration in red blood cells can increase to facilitate the oxygen dissociation in tissues. A compensation mechanism that takes several days or weeks is the increased synthesis of red blood cells.

Iron Metabolism:

With a normal Western diet, 10–15 mg of iron is ingested daily. Under normal circumstances, only 5–10% of this dietary iron is absorbed as Fe2+ in the duodenum or, to a lesser degree, in the jejunum. In severe iron deficiency, the proportion of resorbed iron may increase up to 30%. Iron is lost from the body via sweat, urine, and feces. Iron resorption is improved under the normal acidic and reducing conditions of the gastrointestinal mucosa. The mucosal cells of the duodenum are also capable of resorbing dietary heme iron that later dissociates. Iron resorption can increase severalfold according to the body's demand (e.g., during pregnancy, after an acute blood loss, or in menstruating women). Iron absorption proceeds under the influence of the HFE protein (mutated in hereditary hemochromatosis). Under normal conditions, the HFE protein binds to the transferrin receptor at the cell membrane surface. Both proteins (bound to iron and transferrin) are then imported into the cell. Excess iron can be shed from the mucosal villi of the gut, but if the iron supply continues to exceed iron requirements, iron overload will develop. The most common form is the genetic disorder hemochromatosis, but iron overload can also occur in patients with blood disorders who depend on transfusions. In such patients, iron is deposited in the liver, pancreas, heart muscle, and other organs.

Iron is an essential component of hemoglobin. Most of the iron needed for erythropoiesis does not derive from dietary iron, but is liberated from senescent red blood cells phagocytized by macrophages in the reticuloendothelial system. Iron enters the plasma as Fe3+, where it binds to transferrin and can be used again in erythropoiesis. About 30% of the total body iron is stored in the reticuloendothelial system either as transferrin, ferritin, or hemosiderin. The E-globulin transferrin is synthesized in the liver and can bind two atoms of iron reversibly. Normally, transferrin is only one-third saturated. The progenitor cells of erythropoiesis have specific transferrin receptors, thereby enabling the transfer of iron into these developing erythroid cells.

The Red Blood Cell:

The normal erythrocyte has a diameter of about 8 Pm and a biconcave disc form that provides the red cell with a maximum surface-for-gas exchange as well as optimal deformability. The bipolar lipid layer of the red cell membrane is stabilized on the inner side by the attachment of the structural proteins actin and spectrin. Defects of these proteins lead to hemolytic anemia. The outer layer is covered with mucopolysaccharides that form part of the structure of blood group antigens. The N-acetylneuraminic acid found in these glycoproteins results in a negative charge of the cell surface.

Because red cells have lost their nuclei, they are no longer capable of synthesizing proteins, including enzymes. Red cells remain viable and functional for an

average of 120 d. The necessary energy for red cell metabolism is supplied by the Embden-Meyerhof pathway, which generates adenosine triphosphate by metabolizing glucose to lactate. This anerobic process also results in the formation of nicotinamide-adenine dinucleotide, which is essential for the reduction of methemoglobin to functionnally active hemoglobin.

Hemoglobin is split into globin and heme in the reticuloendothelial system. Both components can be recycled. The globin chains are metabolized into amino acids consequently used for the synthesis of new proteins, and iron is used for further heme synthesis. The remaining protoporphyrin is metabolized to bilirubin. The bilirubin is conjugated in the liver and excreted via bile secretions into the intestine. Intestinal bacteria metabolize bilirubin into stercobilinogen and stercobilin, which are excreted via feces. Part of these hemoglobin degradation products are reabsorbed and excreted via urine as urobilin and urobiliogen [5].

Classification of anemia

Around 2 billion people, amounting to over one 1third of the world's population are anemic. Although anemia is multi-factorial in aetiology, most studies confirmed iron deficiency in > 80 % cases of anemia. It is especially common in women of reproductive age, particularly during pregnancy as the demand for iron increases about 3six to seven fold. WHO reports 35–75% (average 56%) of pregnant women in developing countries and 18% of women from industrialized countries are anemic.

The national health survey of Pakistan reported that 43–47% of rural and 35–40% of urban area is 5suffering from iron deficiency anemia. In our community majority of women start their pregnancy with some degree of iron deficiency anemia because of poor nutrition, short interpregnancy interval, multiparity, abortions, and parasitic infestations In addition, cereal rich diet reduced the bioavailability of iron.

Data from DLHS (District Level Household Survey India) showed that prevalence of moderate and severe anemia was high even among educated 6and high income groups. Although mild anemia is not associated with adverse pregnancy outcome, severe maternal anemia carries significant risk of hemorrhage and infection in the mother. It was found that the relative risk of maternal mortality associated with moderate anemia was 1.35 and for severe anemia was 3.51. It is also associated with preterm birth, low birth her weight and small for gestational age infants, as well as low apgar score and high perinatal mortality. Therefore moderate to severe maternal anemia is a high risk group and it is imperative that all cases of anemia be identified and treated to ensure adequate 9hemoglobin level before labour [6].

Pathophysiology

Inherent in any decision to treat a patient for anemia is an appreciation of the underlying cause of a decrease in the oxygen-carrying capacity of blood. Equally important is an understanding of how this acute or chronic decrease in oxygen delivery affects individual patients. Anemia generally results from blood loss, decreased red blood cell (RBC) production, poor RBC maturation, or increased RBC destruction. This article reviews the pathophysiology of anemia, with specific emphasis on its physiologic consequences in the surgical patient, and provides a contemporary definition of anemia for use in that context. Taking a broader, more functional view of anemia paves the way for understanding and appreciating the newer techniques of RBC conservation and transfusion avoidance, as well as of pharmacologic methods available to counter this disorder.

From the perspective of the surgeon, anemia is not necessarily a diagnosis. It can be viewed as a non- specific sign of disease associated with a low hemoglobin concentration. Traditionally, anemia is de- fined as low values for hematocrit and hemoglobin (for men, <39%, < 13 g/dL, respectively; for women, <36%, < 12 g/dL, respectively). A neoclassical definition, accounting for vascular volume effects and fluid distribution, might be an abnormally. small red blood cell (RBC) mass. In light of our current understanding of oxygen delivery physiology, i.e., the interaction of hemodynamics and oxygen content, both of these definitions are somewhat flawed.

Clearly, the traditional definition fails to account for vascular volume. Although measurements of hemoglobin and hematocrit are easy to accomplish, these values may be of limited use as isolated factors; in combination with vital signs and clinical assessment, however, they may be useful ha clinical management. For example, in acute hemorrhagic hypovolemia the hemoglobin concentration may re- main elevated until equilibration of the vascular space occurs, possibly hours later, or resuscitation intercedes. Acute hypervolemic resuscitation, with large volumes of balanced salt solutions, may dilute the residual blood volume and thereby decrease the hemoglobin concentration. The key point is that acute measurement of hemoglobin concentration may not be useful in assessing oxygen delivery in this situation.

Measuring RBC mass is conceptually a fine idea. Unfortunately, our ability to measure this parameter is limited. Even when it can be assessed, many factors besides the time required and the assumption of steady-state physiology must be considered in interpreting data. In absolute terms, measurement of RBC mass always relates to plasma volume, because current techniques link the two measurements. When plasma volume is increased, the RBC mass is underestimated; this occurs in patients with congestive heart failure, pregnancy, or iatrogenic fluid over- load. Conversely, an overestimate of RBC mass occurs when a patient is dehydrated or when an overaggressive use of diuretics has decreased the plasma volume.

Blood volume loss is a more reasonable definition of anemia; losses of both plasma volume and RBC mass are addressed. Unfortunately, measurement by this definition, too, is related to such

factors as rate of blood loss, whether the loss is acute or chronic, and the degree of vascular refilling. More important, blood volume loss is difficult to measure, especially in patients in unstable condition.

A more contemporary definition of anemia, one reflecting tissue perfusion and oxygen use, is pro- posed. Anemia is here defined as an alteration in the oxygen delivery-oxygen use physiology. In the setting of inadequate oxygen supply or exaggerated use, true acute and chronic physiologic consequences may occur. With adequate oxygen delivery and appropriate oxygen use, homeostasis is attained, and all appropriate compensatory physiologic responses are possible. Obviously, this is an ideal situation. In the chronically ill patient with underlying multiorgan compromise who is receiving a host of pharmacologic agents, normal physiologic responses are blunted or obliterated, limiting the response to altered oxygen delivery. Furthermore, the effects of age on physiologic reserve have a significant impact on the maintenance of adequate oxygen delivery.

To achieve adequate tissue perfusion--the product of flow, cardiac output, and oxygen-carrying capacity-hemoglobin concentration must be relatively constant. Tissues deprived of oxygen are hypoxic and incur an "oxygen debt." That debt, an overuse of oxygen, requires a period of increased oxygen delivery to allow repletion.

Global oxygen delivery is defined as the product of cardiac output and arterial oxygen content. Cardiac output is regulated by preload, contractility, and after load, whereas oxygen content is determined primarily by hemoglobin concentration and, to a lesser extent, by the degree of oxygen saturation. For practical purposes, the relationship between cardiac out- put and arterial oxygen content is assumed to be linear over the usual clinical ranges; it probably is not linear at the physiologic limits of survival.

Thus, global oxygen delivery may be increased by increasing either cardiac output or hemoglobin concentration as needed to attain an oxygen delivery of 500- 700 mL/min/m^2.

The interaction of oxygen delivery with the lungs is described in terms of oxygen saturation. To maintain global oxygen delivery, a decrease; of 15% in oxygen saturation requires a significant increase in cardiac output. Similarly, a greater cardiac compensation, i.e., increased output, is required as the hemoglobin concentration falls.

Global oxygen consumption is the product of cardiac output and the arterial-venous oxygen content difference. Usually, oxygen is consumed at a rate of 125-175 mL/min/m 2, about 25% of the global oxygen delivery. The normal oxygen extraction ratio is 0.25- 0.30. When the ratio exceeds this range by 20-30%, it usually indicates inadequate tissue oxygen delivery and resultant tissue hypoxia and a switch to anaerobic metabolism; the consequent oxygen debt will require replenishment to reestablish homeostasis.

Acute blood loss decreases blood pressure; this triggers release of catecholamines, which in turn produce vasoconstriction, increase cardiac contractility, and increase cardiac output early in the course. This physiologic process normalizes oxygen delivery by increasing blood flow. If bleeding is controlled at its site, the movement of fluid between compartments will lead to blood volume equilibration. However, if blood volume loss continues, vasoconstriction is prolonged, and the subsequent decrease in cardiac output is followed by severe tissue hypoxia, cellular failure, and eventual organ dysfunction and/ or failure. It is this detrimental physiologic cascade that is prevented by ensuring adequate oxygen delivery to tissues.

When oxygen delivery is impaired, another detrimental physiologic cascade occurs at the cellular level. Membrane instability resulting from altered energy production allows sodium and water to flow into the cell, while potassium flows out; cellular edema occurs. Intracellular acidosis, caused by the switch to anaerobic metabolism, will lead to extra- cellular acidemia due to excess lactic acid production. Eventually, the cell loses its structural integrity and dies. This process can be arrested and reversed in an intact cell by an adequate supply of oxygen, achieved by increasing cardiac output and/or adding additional oxygen-carrying capacity.

Anemia (here defined as a decreased RBC mass) is traditionally ascribed to several prominent mechanisms. Whereas all of these mechanisms lead to decreased oxygen-carrying capacity, some produce acute anemia and others a chronic form.

Blood Loss:

Acute bleeding often accompanies trauma. However, it may also be caused by acute or chronic gastrointestinal hemorrhage (secondary to ulcer, inflammatory bowel disease, tumor, or infection), intraoperative blood loss, and excessive phlebotomy for diagnostic purposes.

Iron Deficiency:

Blood loss is the single most important cause of iron deficiency. When blood is lost externally, a cycle of negative iron balance begins: output exceeds in- put. Eventually, the lack of iron stores becomes the limiting factor in erythropoiesis. Failure of erythropoiesis is usually due to iron deficiency but is also associated with renal disease (erythropoietin deficiency), endocrine disorders (e. g., thyroid and pituitary disease), and heavy metal toxicity.

Chronic Illness or Inflammation:

The anemia of chronic illness and inflammation is now assumed to be in part a defect of iron metabolism. Decreased RBC survival, an impaired marrow response, and evidence of disturbed iron metabolism have been documented in persons with this type of anemia. In addition, there is some evidence of a disturbance in monocyte- macrophage release of iron that may be related to inflammatory cytokines. If this hypothesis is validated, the anemia of chronic illness or inflammation may be a rarity due to a state of functional iron deficiency. Moreover, cytokines

may decrease the responsiveness of erythroid precursors to erythropoietin, as well as decrease erythropoietin production by the kidney or increase its rate of catabolism. In general, serum erythropoietin levels are inappropriately low for the degree of anemia in patients with the anemia of chronic disease.

Hemolysis, Marrow Failure, and Megaloblastosis:

Anemia due to decreased RBC production results from failure of the bone marrow to produce adequate numbers of mature red cells, as may occur in aplastic anemia. In addition, failure to produce an adequate number of mature red cells may occur in conditions such as thalassemia and vitamin B_{12} or folate deficiency, despite hyperplastic bone marrow; much of the erythroid activity of patients with these conditions is "ineffective."

Increased RBC destruction can also lead to a de- crease in RBC mass. The causes of increased extra- vascular RBC destruction include various inmmno- hemolytic diseases, hereditary spherocytosis, associated hemoglobinopathies, and enzyme deficiencies. Since surgeons often see patients with these underlying illnesses, they must recognize such disorders and use them as the basis for transfusion decisions when appropriate.

Intravascular destruction of RBCs (lysis) can re- sult from a hemolytic transfusion reaction (lethal in approximately 1 per 100,000 transfusions), burns, infection (e.g., malaria or infection with Clostridium perfringens), or fresh-water drowning, or RBC lysis may occur in patients who are deficient in glucose- 6-phosphate dehydrogenase and thus unable to metabolize various drugs. Distinctly uncommon, the results of intravascular hemolysis can range from mild reactions to severe or even lethal consequences. Cardiopulmonary bypass circuits and intraoperative cell salvage techniques can also contribute to RBC destruction, but rarely to an extent requiring intervention. Although cardiopulmonary bypass circuits can fragment RBCs and produce secondary hemolysis, the filters in the devices are usually sufficiently effective to obviate problems.

These underlying mechanisms of anemia rarely require surgical intervention, except for splenectomy to manage spherocytosis or thalassemia. However, if an acute surgical problem develops in a patient with one of these illnesses, an understanding of the cause of the anemia and its pathophysiology will be helpful in guiding management.

Further exploration is needed to elucidate the role of iron deficiency (due to chronic blood loss or in- adequate intake) during postoperative recovery. If recovery is related to the rate of restoration of RBC mass, intravascular volume, and normalization of cardiovascular homeostatic mechanisms, then sufficient iron stores are necessary to optimize erythropoiesis [7].

Hemolytic anemia

Hemolysis presents as acute or chronic anemia, reticulocytosis, or jaundice. The diagnosis is established by reticulocytosis, increased unconjugated bilirubin and lactate dehydrogenase, decreased haptoglobin, and peripheral blood smear findings. Premature destruction of erythrocytes occurs intravascularly or extravascularly. The etiologies of hemolysis often are categorized as acquired or hereditary. Common acquired causes of hemolytic anemia are autoimmunity, microangiopathy, and infection. Immune-mediated hemolysis, caused by antierythrocyte antibodies, can be secondary to malignancies, autoimmune disorders, drugs, and transfusion reactions. Microangiopathic hemolytic anemia occurs when the red cell membrane is damaged in circulation, leading to intravascular hemolysis and the appearance of schistocytes. Infectious agents such as malaria and babesiosis invade red blood cells. Disorders of red blood cell enzymes, membranes, and hemoglobin cause hereditary hemolytic anemias. Glucose-6-phosphate dehydrogenase deficiency leads to hemolysis in the presence of oxidative stress. Hereditary spherocytosis is characterized by spherocytes, a family history, and a negative direct antiglobulin test. Sickle cell anemia and thalassemia are hemoglobinopathies characterized by chronic hemolysis.

Hemolysis is the destruction or removal of red blood cells from the circulation before their normal life span of 120 days. While hemolysis can be a lifelong asymptomatic condition, it most often presents as anemia when erythrocytosis cannot match the pace of red cell destruction. Hemolysis also can manifest as jaundice, cholelithiasis, or isolated reticulocytosis.

There are two mechanisms of hemolysis. Intravascular hemolysis is the destruction of red blood cells in the circulation with the release of cell contents into the plasma. Mechanical trauma from a damaged endothelium, complement fixation and activation on the cell surface, and infectious agents may cause direct membrane degradation and cell destruction.

The more common extravascular hemolysis is the removal and destruction of red blood cells with membrane alterations by the macrophages of the spleen and liver. Circulating blood is filtered continuously through thin-walled splenic cords into the splenic sinusoids (with fenestrated basement membranes), a spongelike labyrinth of macrophages with long dendritic processes.[1] A normal 8-micron red blood cell can deform itself and pass through the 3-micron openings in the splenic cords. Red blood cells with structural alterations of the membrane surface (including antibodies) are unable to traverse this network and are phagocytosed and destroyed by macrophages.

Anemia most often is discovered through laboratory tests, but the history and physical examination can provide important clues about the presence of hemolysis and its underlying cause. The patient may complain of dyspnea or fatigue (caused by anemia). Dark urine and, occasionally, back pain may be reported by patients with intravascular hemolysis. The skin may appear jaundiced or pale. A resting tachycardia with a flow murmur may be present if the anemia

is pronounced. Lymphadenopathy or hepatosplenomegaly suggest an underlying lymphoproliferative disorder or malignancy; alternatively, an enlarged spleen may reflect hypersplenism causing hemolysis. Leg ulcers occur in some chronic hemolytic states, such as sickle cell anemia.

Diagnostic Testing:

HEMATOLOGIC TESTS:

Along with anemia, a characteristic laboratory feature of hemolysis is reticulocytosis, the normal response of the bone marrow to the peripheral loss of red blood cells. In the absence of concomitant bone marrow disease, a brisk reticulocytosis should be observed within three to five days after a decline in hemoglobin. In a minority of patients, the bone marrow is able to chronically compensate, leading to a normal and stable hemoglobin concentration. The anemia of hemolysis usually is normocytic, although a marked reticulocytosis can lead to an elevated measurement of mean corpuscular volume, because the average mean corpuscular volume of a reticulocyte is 150 fL.

Review of the peripheral blood smear is a critical step in the evaluation of any anemia. Along with an assessment for pathognomonic red blood cell morphologies, such as spherocytes or schistocytes, examination of the white blood cells and platelets for coexisting hematologic or malignant disorders is essential.

CHEMISTRY TESTS:

The destruction of red blood cells is characterized by increased unconjugated bilirubin, increased lactate dehydrogenase, and decreased haptoglobin levels. Lactate dehydrogenase and hemoglobin are released into the circulation when red blood cells are destroyed. Liberated hemoglobin is converted into unconjugated bilirubin in the spleen or may be bound in the plasma by haptoglobin. The hemoglobin-haptoglobin complex is cleared quickly by the liver, leading to low or undetectable haptoglobin levels.

URINARY TESTS:

In cases of severe intravascular hemolysis, the binding capacity of haptoglobin is exceeded rapidly, and free hemoglobin is filtered by the glomeruli. The renal tubule cells may absorb the hemoglobin and store the iron as hemosiderin; hemosiderinuria is detected by Prussian blue staining of sloughed tubular cells in the urinary sediment approximately one week after the onset of hemolysis. Hemoglobinuria, which causes red-brown urine, is indicated by a positive urine dipstick reaction for heme in the absence of red blood cells.

Acquired Disorders:

Once the diagnosis of hemolysis is made on the basis of laboratory and peripheral smear findings, it is necessary to determine the etiology. While most forms of hemolysis are classified as predominantly intravascular or extravascular, the age of onset, accompanying clinical presentation, and co-existing medical problems usually guide the clinician to consider either an acquired or a hereditary cause.

IMMUNE HEMOLYTIC ANEMIA:

Immune hemolytic anemias are mediated by antibodies directed against antigens on the red blood cell surface. Microspherocytes on a peripheral smear and a positive direct antiglobulin test are the characteristic findings. Immune hemolytic anemia is classified as autoimmune, alloimmune, or drug-induced, based on the antigen that stimulates antibody- or complement-mediated destruction of red blood cells.

AUTOIMMUNE HEMOLYTIC ANEMIA:

Autoimmune hemolytic anemia (AIHA) is mediated by autoantibodies and further subdivided according to their maximal binding temperature. Warm hemolysis refers to IgG autoantibodies, which maximally bind red blood cells at body temperature (37°C [98.6°F]). In cold hemolysis, IgM autoantibodies (cold agglutinins) bind red blood cells at lower temperatures (0° to 4°C [32° to 39.2°F]).

When warm autoantibodies attach to red blood cell surface antigens, these IgG-coated red blood cells are partially ingested by the macrophages of the spleen, leaving microspherocytes, the characteristic cells of AIHA. These spherocytes, which have decreased deformability compared with normal red blood cells, are trapped in the splenic sinusoids and removed from circulation.

Cold autoantibodies (IgM) temporarily bind to the red blood cell membrane, activate complement, and deposit complement factor C3 on the cell surface. These C3-coated red blood cells are cleared slowly by the macrophages of the liver (extravascular hemolysis). Less frequently, the complete complement cascade is activated on the cell surface, resulting in the insertion of the membrane attack complex (C5b to C9) and intravascular hemolysis.

The direct antiglobulin test (DAT), also known as the direct Coombs' test, demonstrates the presence of antibodies or complement on the surface of red blood cells and is the hallmark of autoimmune hemolysis.The patient's red blood cells are mixed with rabbit or mouse antibodies against human IgG or C3. Agglutination of the patient's antibody- or complement-coated red blood cells by anti-IgG or anti-C3 serum constitutes a positive test. Red blood cell agglutination with anti-IgG serum reflects warm AIHA, while a positive anti-C3 DAT occurs in cold AIHA.

Although most cases of autoimmune hemolysis are idiopathic, potential causes should always be sought. Lymphoproliferative disorders (e.g., chronic lymphocytic leukemia, non-Hodgkin's

lymphoma) may produce warm or cold autoantibodies. A number of commonly prescribed drugs can induce production of both types of antibodies. Warm AIHA also is associated with autoimmune diseases (e.g., systemic lupus erythematosus), while cold AIHA may occur following infections, particularly infectious mononucleosis and *Mycoplasma pneumoniae* infection. Human immunodeficiency virus infection can induce both warm and cold AIHA.

AIHA should be managed in conjunction with a hematologist. Corticosteroids (and treatment of any underlying disorder) are the mainstay of therapy for patients with warm AIHA. Refractory cases may require splenectomy, intravenous gamma globulin, plasmapheresis, cytotoxic agents, or danazol (Danocrine). All of the aforementioned therapies are generally ineffective for cold AIHA, which is managed most effectively by avoidance of the cold and treatment of any underlying disorder. Transfusion therapy in AIHA is challenging, and the most compatible red blood cells (i.e., those with the least cross-reacting antibodies) should be given.

DRUG-INDUCED HEMOLYTIC ANEMIA:

Drug-induced immune hemolysis is classified according to three mechanisms of action: drug-absorption (hapten-induced), immune complex, or autoantibody. These IgG- and IgM-mediated disorders produce a positive DAT and are clinically and serologically indistinct from AIHA.

Hemolysis resulting from high-dose penicillin therapy is an example of the drug-absorption mechanism, in which a medication attached to the red blood membrane stimulates IgG antibody production. When large amounts of drug coat the cell surface, the antibody binds the cell membrane and causes extravascular hemolysis.

Quinine-induced hemolysis is the prototype of the immune complex mechanism, in which the drug induces IgM antibody production. The drug-antibody complex binds to the red blood cell membrane and initiates complement activation, resulting in intravascular hemolysis.

Alpha-methyldopa is the classic example of antierythrocyte antibody induction. Although the exact mechanism is unknown, the drug (perhaps by altering a red blood cell membrane protein and rendering it antigenic) induces the production of antierythrocyte IgG antibodies and causes an extravascular hemolysis.

ALLOIMMUNE (TRANSFUSION) HEMOLYTIC ANEMIA:

The most severe alloimmune hemolysis is an acute transfusion reaction caused by ABO-incompatible red blood cells. For example, transfusion of A red cells into an O recipient (who has circulating anti-A IgM antibodies) leads to complement fixation and a brisk intravascular hemolysis. Within minutes, the patient may develop fever, chills, dyspnea, hypotension, and shock.

Delayed hemolytic transfusion reactions occur three to 10 days after a transfusion and usually are caused by low titer antibodies to minor red blood cell antigens. On exposure to antigenic blood cells, these antibodies are generated rapidly and cause an extravascular hemolysis. Compared with the acute transfusion reaction, the onset and progression are more gradual.

MICROANGIOPATHIC HEMOLYTIC ANEMIA:

Microangiopathic hemolytic anemia (MAHA), or fragmentation hemolysis, is caused by a mechanical disruption of the red blood cell membrane in circulation, leading to intravascular hemolysis and the appearance of schistocytes, the defining peripheral smear finding of MAHA.

When red blood cells traverse an injured vascular endothelium—with associated fibrin deposition and platelet aggregation—they are damaged and shredded. This fragmentation occurs in a diverse group of disorders, including thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, preeclampsia, eclampsia, malignant hypertension, and scleroderma renal crisis. In addition, intravascular devices, such as prosthetic cardiac valves and transjugular intrahepatic portosystemic shunts, can induce MAHA.

INFECTION:

Numerous mechanisms link infection and hemolysis. Autoantibody induction (e.g., by *M. pneumoniae*), glucose-6-phosphate dehydrogenase (G6PD) deficiency, and antimicrobial drugs (e.g., penicillin) are discussed elsewhere in this article. In addition, certain infectious agents are directly toxic to red blood cells.

Malaria is the classic example of direct red blood cell parasitization. Plasmodium species, introduced by the Anopheles mosquito, invade red blood cells and initiate a cycle of cell lysis and further parasitization. Both the cellular invasion and the metabolic activity of the parasite alter the cell membrane, leading to splenic sequestration. Red cell lysis also contributes to the anemia and can be dramatic in the case of "black water fever," named for the brisk intravascular hemolysis and hemoglobinuria that accompany overwhelming *Plasmodium falciparum* infection. The diagnosis is made by the observation of intracellular asexual forms of the parasite on thick and thin blood smears.

Similarly, *Babesia microti* and *Babesia divergens*, tick-borne protozoa, and *Bartonella bacilliformis*, a gram-negative bacillus transmitted by the sandfly, cause extravascular hemolysis by direct red blood cell invasion and membrane alteration.

Septicemia caused by *Clostridium perfringens*, which occurs in intra-abdominal infections and septic abortions, causes hemolysis when the bacterium releases alpha toxin, a phospholipase that degrades the red blood cell membrane.

Hereditary Disorders:

The mature red blood cell, while biochemically complex, is a relatively simple cell that has extruded its nucleus, organelles, and protein-synthesizing machinery. Defects in any of the remaining components—enzymes, membrane, and hemoglobin—can lead to hemolysis.

ENZYMOPATHIES:

The most common enzymopathy causing hemolysis is G6PD deficiency. G6PD is a critical enzyme in the production of glutathione, which defends red cell proteins (particularly hemoglobin) against oxidative damage. This X-linked disorder predominantly affects men. More than 300 G6PD variants exist worldwide, but only a minority cause hemolysis.

Most patients have no clinical or laboratory evidence of ongoing hemolysis until an event—infection, drug reaction or ingestion of fava beans—causes oxidative damage to hemoglobin. The oxidized and denatured hemoglobin cross-links and precipitates intracellularly, forming inclusions that are identified as Heinz bodies on the supravital stain of the peripheral smear. Heinz bodies are removed in the spleen, leaving erythrocytes with a missing section of cytoplasm; these “bite cells” can be seen on the routine blood smear. The altered erythrocytes undergo both intravascular and extravascular destruction. Older red blood cells are most susceptible, because they have an intrinsic G6PD deficiency coupled with the normal age-related decline in G6PD levels.

Hemolysis occurs two to four days following exposure and varies from an asymptomatic decline in hemoglobin to a marked intravascular hemolysis. Even with ongoing exposure, the hemolysis usually is self-limited, as the older G6PD-deficient cells are destroyed. There is no specific therapy other than treatment of the underlying infection and avoidance of implicated medications. In cases of severe hemolysis, which can occur with the Mediterranean-variant enzyme, transfusion may be required.

G6PD activity levels may be measured as normal during an acute episode, because only non hemolyzed, younger cells are assayed. If G6PD deficiency is suspected after a normal activity-level measurement, the assay should be repeated in two to three months, when cells of all ages are again present.

MEMBRANOPATHIES:

Hereditary spherocytosis is an autosomal dominant disorder caused by mutations in the red blood cell membrane skeleton protein genes. With a weakened protein backbone anchoring its lipid bilayer, the membrane undergoes a progressive deterioration in structure, resulting in a spherocyte, the characteristic abnormality seen on peripheral smear. As with AIHA, the spherocytes are unable to pass through the splenic cords and are degraded and ingested by the monocyte-macrophage system.

Although there is marked variability in phenotype, hereditary spherocytosis is typically a chronically compensated, mild to moderate hemolytic anemia. The diagnosis is based on the combination of spherocytosis noted on peripheral smear, a family history (in 75 percent of cases), and a negative DAT. The mean corpuscular hemoglobin concentration frequently is elevated.

Splenectomy effectively arrests the extravascular hemolysis and prevents its long-term complications, such as cholelithiasis and aplastic crises. Because of the inherent risk of infections and sepsis, however, splenectomy generally is reserved for use in patients older than five years with moderate to severe disease, characterized by hemoglobin concentrations of less than 11 g per dL (110 g per L) and jaundice. Partial splenectomy has been demonstrated to be effective in decreasing hemolysis while maintaining the phagocytic function of the spleen.

HEMOGLOBINOPATHIES:

Chronic hemolysis can be a characteristic of disorders of hemoglobin synthesis, including sickle cell anemia and thalassemias.

The thalassemias are a heterogeneous group of inherited multifactorial anemias characterized by defects in the synthesis of the alpha or beta subunit of the hemoglobin tetramer ($\alpha_2\beta_2$). The deficiency in one globin chain leads to an overall decrease in hemoglobin and the intracellular precipitation of the excess chain, which damages the membrane and leads to clinically evident hemolysis in the severe forms of alpha thalassemia (hemoglobin H disease) and beta thalassemia (intermedia and major). Beta thalassemia can be diagnosed by hemoglobin electrophoresis, which shows elevated levels of hemoglobins A_2 and F, while diagnosis of alpha thalassemia requires genetic studies. Thalassemias are characterized by hypochromia and microcytosis; target cells frequently are seen on the peripheral smear.

Sickle cell anemia is an inherited disorder caused by a point mutation leading to a substitution of valine for glutamic acid in the sixth position of the β chain of hemoglobin. Membrane abnormalities from sickling and oxidative damage caused by hemoglobin S, along with impaired

deformability of sickle cells, leads to splenic trapping and removal of cells. Some degree of intravascular hemolysis occurs as well. Hemoglobin electrophoresis reveals a predominance of hemoglobin S. Sickle cells are observed on the peripheral smear [8].

THE HEREDITARY ANEMIAS

The anemias which have in common a hereditary factor are characterized by an intracorpuscular defect, and are hemolytic in type. With the exception of thalassemia the anemia is normocytic and normochromic. No extracorpuscular defect has been found to be present except where a complicating factor of "hypersplenism" has developed later on in the course of the disease. These important facts have been established by studies of the life span of the red blood cells. When the erythrocytes of the patient have been transfused into normal recipients, life spans of fourteen to sixty days, instead of the normal I2o days, have been found. This, then, constitutes an intracorpuscular defect. Conversely, normal erythrocytes transfused into these patients survive for I20 days; andthus the absence of an extracorpuscular defect is established.

Shortened survival of the patient's red blood cells implies rapid hemolysis within the body. This results in an increase of fecal and urinary urobilinogen, and of the serum bilirubin, largely of the "indirect" fraction. The bone marrow responds to the demand for more red blood cells by a heightened production, as is reflected in an increase of the reticulocytes. If the bone marrow is placed under unusually severe stress, normoblasts, and even increased numbers of leukocytes and platelets will appear in the peripheral blood. These evidences of increased blood destruction and production must always be looked for when one suspects a hemolytic anemia.

Many painstaking genealogic studies of the patients and their families have shown that in the case of congenital hemolytic anemia, ovalocytosis, and hereditary nonspherocytic hemolytic anemia, the disease is inherited as a Mendelian dominant from either parent. In the case of thalassemia and sicklemia homozygosity of the abnormal gene results in the expression of the disease, and heterozygosity, the trait. It is not surprising, in view of the fact that the defect lies within the red blood cell, that this defect has been shown to be due to an abnormal hemoglobin in certain of these anemias. Indeed, as more delicate techniques are discovered for studying the complexities of the arrangement of the protein constituents of the erythrocyte, it may be expected that eventually all of the members of this group of "hereditary anemias" will be shown to have abnormalities of the hemoglobin or of the supporting stroma.

Types of hereditary anemias:

CONGENITAL HEMOLYTIC ANEMIA:

Mechanism: In congenital hemolytic anemia the abnormal red blood cell manifests itself as a spherocyte, which is inherited as a Mendelian dominant from either parent. A spherocyte is so constructed as to have the largest amount of volume for the smallest amount of surface. All red cells behave as osmometers and take in extra water under circumstances of stagnation such as occur in the spleen. The biconcave shape of the normal erythrocyte is especially adapted to withstand the stress of swelling; whereas the spherocyte, having no expandable surface for its volume, will have to rupture when extra water enters it. Osmotic fragility studies2 not only demonstrate the increased osmotic fragility of the spherocyte in the peripheral blood, but also

show that it is further increased after stasis within the spleen. It has also been shown2'3 that when these patients are transfused with normal red cells the spleen has a preference for trapping the patient's spherocytes rather than the normal cells. This is a second reason for the enlarged spleen being a graveyard for the patient's erythrocytes.

Dr. Castle has emphasized the point that increased osmotic fragility alone will not explain the destruction of erythrocytes in vivo because the body fluids have a tonicity equivalent to that of o.85 per cent NaCl, and in most cases of congenital hemolytic anemia the hemolysis in hypotonic saline does not begin until 0.75 per cent NaCl or lower. (The hemolysis of normal erythrocytes begins at about 0.44 per cent NaCl.) His group' showed that the "mnecharnical fragility" of the spherocyte is also increased, and postulated that in vivo hemolysis is probably the result of the mechanical buffeting of the erythrocyte as it traverses the narrow capillaries at high speed. Splenectomy abolishes the anemia in these patients by removing the organ which increases the osmotic swelling, and therefore the mechanical fragility, of the erythrocyte to the critical bursting point.

Although the osmotic and mechanical fragility of the red cells is somewhat reduced by splenectomy, the original spherocytosis is unchanged. This is to be expected since the inherent defect is hereditary and is an intrinsic part of the cell. Electrophoretic studies have failed to show the presence of an abnormal hemoglobin.The exact defect within the erythrocyte is quite unknown, and may even reside in the stroma rather than within the hemoglobin.

Clinical Picture: What are the manifestations of this disease? Although symptoms would be expected to be manifested in early childhood because the spherocytosis is presumably present at birth, for unknown reasons, the disease may not be clinically apparent until early, or even late, adult life. The only symptoms present are usually those referable to anemia. The patient is often jaundiced. Since the anemia may be mild, the aphorism has arisen: "more jaundiced than anemic." The diagnosis is made by the finding of splenomegaly, a hemolytic type of anemia, and spherocytosis. A negative Coombs test and the presence of spherocytosis in one of the parents will further distinguish this disease from the spherocytic hemolytic anemia of the acquired type. In the occasional case where the spherocytosis is minimal and the osmotic fragility is normal, incubation of the blood for eighteen to twenty-four hours will increase the osmotic fragility much more than that of the erythrocytes of a normal person. (Incubation in the test tube is the in vitro equivalent of in vivo stagnation of blood in an enlarged spleen.).

Treatment: The treatment of choice is splenectomy since a clinical cure of the anemia can be expected in all cases.

THALASSEMIA MAJOR AND MINOR:

Mechanism: The relationship of thalassemia major (Cooley's anemia) to thalassemia minor ("familial microcytic anemia", "target cell anemia").

was not well defined until the extensive genetic studies of Valentine and Neel5 in I1944 indicated that the former is the homozygous and the latter the heterozygous manifestation of the anomaly. In other words, inheritance of the abnormal gene from only one parent would result in heterozygosity and therefore in the relatively benign manifestations of thalassemia minor; whereas inheritance of the abnormal gene from both parents would result in homozygosity and therefore in the serious form of the disease, thalassemia major. The great majority of cases have occurred in persons whose ancestry has stemmed from countries bordering the Mediterranean Sea, e.g., in Italians, Greeks, Armenians and Syrians, and presumably indicates genetic connections. However, there are a few reports of Chinese, Indian and Negro patients.

The abnormal erythrocyte is a very small, flat hypochromic cell which appears defective in hemoglobin. The similarities of this microcytic hypochromic anemia to that of iron deficiency anemia are so striking that it seems that there must be some fundamental error in iron metabolism in this disease. This hypothesis is further borne out by the finding of iron deposition in organs, distributed as in hemochromatosis rather than as in hemosiderosis. The flat erythrocyte has a greatly increased resistance to hypotonic saline - (a platycyte being the reverse of a spherocyte)-but it has an increased mechanical fragility and a shortened life span.

In addition to the hemolytic component there seems to be an added component of decreased capacity of blood formation, despite the morphological appearance of normoblastic hyperplasia of the bone marrow. This is shown by the fact that the reticulocytosis is much more inconstant, and of a lesser degree, than in other types of hemolytic anemias. Indeed, it is not uncommon for the reticulocytes to be normal or low even when there are many normoblasts in the peripheral blood. Many patients who are transfused frequently have few remaining circulating cells of their own blood type. In this respect they more closely resemble patients with an erythropoietic arrest such as pernicious anemia than those with "pure" hemolytic anemias, such as sickle cell anemia. It is tempting to postulate that there is a maturation arrest at the level of the basophilic normoblast because of the relative inability to incorporate iron into the hemoglobin molecule. It is interesting that basophilic and polychromatophilic normoblasts are abundant in the marrow, whereas the hemoglobin-containing orthochromatic normoblast is scarce.

Recently Singer6 has shown that there is a persistence of a fetal type of hemoglobin in the red cells in most of these patients, and we have also found that to be so in the course of our studies. Fetal (F) hemoglobin, in contrast to normal (A) hemoglobin, is characterized by a marked resistance to denaturation by alkalis. It has been known that the erythrocytes at birth contain about 80% fetal hemoglobin.This is gradually replaced by normal hemoglobin, so that at the age of four months only about io per cent remains, and at the age of one year there is usually none left. The presence of fetal hemoglobin can be demonstrated in both thalassemia major and minor, usually in small amounts, but sometimes in quantities as high as 49%. There is not a good quantitative correlation between the amount of fetal hemoglobin and the severity of the disease. Although the exact significance of fetal hemoglobin is unknown, this is evidence of another abnormality within the hemoglobin itself. Since fetal hemoglobin has been found in a variety of

anemias, its presence is thought to be the non-specific result of anemic stress on hemoglobin formation with a partial reversion to fetal pathways. Electrophoretic studies of the hemoglobin of patients with thalassemia have so far not shown any abnormalities in addition to those of a persistence of fetal hemoglobin.

Clinical Picture:

Thalassemia major: This disease is a very serious one with a short life expectancy. The patients develop a severe anemia requiring transfusions by about the second year of life. The marked expansion of the marrow cavity of the malar bones produces the "mongoloid" facies; the generalized marrow changes with their secondary effects on the growing bones produce typical x-ray changes. The spleen and liver may become so large as to cause great protuberance of the abdomen. The patient lives an abnormal life at best, having to come to the hospital or clinic for transfusions as often as every two weeks. Death usually intervenes by puberty, as a result of intercurrent infection or of liver or cardiac insufficiency due to hemochromatosis. The diagnosis is easily made in a child of Mediterranean ancestry, who has hepatosplenomegaly, bone changes in the x-rays, and a microcytic hypochromic anemia, with red cells which appear fragmented and which have a marked resistance to hypotonic saline solutions. Occasionally a relatively mild case may simulate the anemia of iron deficiency, but can be differentiated by the lack of response to iron therapy.

The only treatment is supportive and consists mainly of blood transfusions. Splenectomy has been shown to ameliorate the anemia in some cases by diminishing the transfusion requirement. Dr. Lichtman8 has recently found that the favorable effect of splenectomy occurs in patients who have developed an extracorpusccular defect as demonstrated by a shortened survival time of normal transfused erythrocytes. This is corrected by splenectomy, thus diminishing the need for blood transfusions. However, since splenectomy does not alter the intracorpuscular defect, it is by no means curative, nor has it been ascertained as to whether it lengthens the longevity of the patient.

Thalassemia mninor: This diagnosis is usually based on the results of a chance blood examination of an asymptomatic individual. The findings often consist of a low hemoglobin value and a high red cell count (i.e., a "microcytic polycythemia"), and an increased resistance of the erythrocytes to hypotonic saline. The red cells may have a normal life span. This diagnosis, of course, necessitates no treatment, and the physician should be urged to refrain from producing an "anemic neurosis" in his patient-as is not uncommon! However, there are also many gradations of thalassemia minor, including a shortened red cell survival." These gradations suggest that the thalassemia gene possesses varying degrees of penetrance.

SICKLE CELL ANEMIA:

Mechanism: In sickle cell anemia the abnormality of the red cell is characterized by its transformation from a biconcave disc to a "sickled" cell when oxygen tension is lowered so that

the hemoglobin is in the reduced state. It has long been known that 8% of American Negroes have red cells that can be sickled in vitro and have no anemia or symptoms-i.e., have the "sickle cell trait." About 0.2% have sickle cell anemia, a condition in which the cells can assume the sickled form in vivo as well as in vitro. A basic understanding of the difference between sickle cell anemia and sickle cell trait appeared with Neel's clarification of the hereditary factors'0 and Pauling's demonstration" of an abnormal hemoglobin by electrophoretic methods.

Neel showed that sickle cell trait is the expression of heterozygosity of the sickle cell gene and that sickle cell anemia is the expression of homozygosity. For example if there is a mating of two individuals possessing the sickle cell trait, and if they have four children, one child of the four may have sickle cell anemia, two of the four have sickle cell trait, and one may be normal. Almost 99% of the cases reported have been in Negroes. The majorities of those reported in whites have been Italians or Greeks, and are thought to represent old genetic connections between the peoples of the two shores of the Mediterranean Sea.

Pauling's revolutionary findings published almost simultaneously with Neel's in 1949 showed that the hemoglobin (S) of sickle cells has a different electrophoretic mobility from normal (A) hemoglobin. In sickle cell anemia, all of the hemoglobin is abnormal in this respect; whereas in sickle cell trait 27-44 per cent of the hemoglobin is S hemoglobin and the remainder of the hemoglobin is normal (A). This obviously fits in very well with the hereditary features just mentioned. The fact that the S hemoglobin is less than 50 per cent may be explained 'by the hypothesis that the presence of normal hemoglobin in sickle cell trait interferes with complete penetrance of the sickle gene. Electrophoretic studies of heme and denatured globin from S hemoglobin show no abnormalities, but recently studies of natural globins'2 have revealed differences from the normal. X-ray diffraction studies of S and normal hemoglobin crystals are identical. Hence, it is thought that the defect in S hemoglobin may consist in a slightly different arrangement of the basic constituents of the globin portion of the molecule.

Harris13 has shown that reduced S hemoglobin has a very high' viscosity and has a "tactoid" formation which can be observed with the phase microscope. Tactoids are oriented masses of molecules. Perutz'4 has postulated that the change into the sickled shape is the result of crystal formation of S hemoglobin which occurs in the reduced state because of its very low solubility in that form. Reduced S hemoglobin is so insoluble that only I/7 of it can stay in solution when oxyhemoglobin changes to reduced hemoglobin. Reduced S hemoglobin was found to have only one-hundredth of the solubility of the oxy-S compound, whereas reduced normal (A) hemoglobin had one-half the solubility of the oxy-A compound. These considerations give us some insight into the dynamics of the extraordinary distortion of the biconcave disc that occurs in the sickling process.

The high viscosity of S hemoglobin in its reduced and relatively insoluble state and the high viscosity which is the inevitable result of the sickle cell shape explains one of the worst manifestations of the disease-capillary thrombosis. It is in the capillaries where the 02 tension

falls to its lowest with the production of reduced hemoglobin, so that it is in the capillaries where the sickling takes place with consequent slowing of blood flow due to the increased viscosity. Mass capillary blockade may stop circulation with death of a part, or all, of the organ involved. It is this complication rather than the anemia per se that gives rise to the most distressing symptoms of the disease and eventually to death itself. It has been shown4 that the mechanical fragility of the cell in the sickled form is many times that of the biconcave disc, so the mechanism of the anemia is also explained by the peculiarity of the sickled shape.

In the case of sickle cell trait there is not enough S hemoglobin in the cell to produce sickling at the lowest 02 tension (40 mm.) that can occur within the body. It is only in vitro, at artificial levels of much lower 02 tension (i 8 mm. or less) that the cells can be changed into the sickle shape. Obviously, under these circumstances no damage can be done in vivo, and the person with sickle cell trait will have no anemia and no symptoms.

Recently new questions have arisen because studies in Africa have shown that some tribes have an incidence of sickle cell trait of as high as 40% whereas sickle cell anemia is rare or non-existent. This apparent contradiction to the homozygous theory has been explained'5 by postulating that admixture of white "A" genes alters the penetrance of the Negro S gene and thus allows the manifestations of sickle cell anemia! At any rate, much more study is necessary to elucidate these problems. As usual, the solving of one problem opens the door to many more unsolved problems.

Singer" has shown that most of his patients with sickle cell anemia have fetal hemoglobin, but that those with sickle cell trait had none.

There was no correlation between the severity of the disease and the amount of the fetal hemoglobin. We have found fetal hemoglobin present in significant amounts in only a few of our patients with sickle cell anemia, the highest value being 39.8%" It is thought that the stress of anemia may cause the organism to resort to old (fetal) methods of producing hemoglobin. However, at birth when there is a high percentage of fetal hemoglobin, infants with sickle cell trait have only a low percentage of sickle cells and do not develop 100% of sickle cells until the age of four months, at a time when fetal hemoglobin has almost disappeared. This apparent inability of fetal hemoglobin to sickle may be an important reason for the great rarity of manifestations of clinical sickle cell anemia in the first six months of life.

Clinical Picture: Sickle cell anemia is diagnosed hematologically by the presence of a hemolytic type of anemia, the finding of target cells and a few "irreversible" sickle forms in the stained smear, and ioo per cent sickling in a special preparation in which 02 tension is reduced by some means (e.g., by sealing with vaseline, reduction with N_2 or H_2 gas, or by reduction with a reducing agent such as sodium bisulphite).

Symptoms are rare in the first six months of life, but are present in half of the cases by the age of two years. Fatigue and irritability occur as a non-specific reflection of the anemia. The more

troublesome Symptoms are those which can be attributed to the sickling process itselfi.e., bone and joint pain and abdominal pain and fever. Severe bouts of trouble are known as "crises" and often occur without exacerbation of the hemolytic anemia, and without any known precipitating cause. Many older patients attribute the onset of a crisis to emotional disturbances at home. These points to the vascular factor involved (and may be somewhat analogous to attacks of cardiac decompensation in hypertensives). Death may occur in crisis as a result of insufficiency of any vital organ, such as the brain, lung, liver or kidney. Involvement of the bones leads to typical x-ray lesions' and may cause severe pain. Intractable leg ulcers may follow slight trauma and are presumably due to the poor circulation in those areas, complicated by the sluggish flow of sickled cells. Although the spleen often becomes abnormally small because of auto-infarction from sickling within the spleen, this organ may also be enlarged and even give rise to a superadded factor of "hypersplenism."

Treatment: There is no satisfactory treatment, other than supportive, at present. Transfusions should be given for symptoms due to anemia only. The administration of nasal oxygen does not result in clinical improvement and may actually intensify the anemia as a result of the suppression of blood formation. Cortisone and ACTH have been tried with quite variable results, and are of limited value at best. The same can be said for vasodilators.

OTHER ANEMIAS WITH ABNORMAL HEMOGLOBINS:

In the course of doing genetic studies of the families of Negro patients with sickle cell disease two other hemoglobins, designated C and D,have been discovered. Neither has the ability to produce sickling. Hemoglobin D possesses the same electrophoretic mobility as S hemoglobin, but has the same solubility as normal A hemoglobin. (Reduced S hemoglobin has only I/I4 the solubility of A hemoglobin in the reduced state.) Hemoglobin C in filter paper electrophoresis migrates very slowly, much slower than S hemoglobin, which in turn migrates more slowly than normal hemoglobin.

Any combination of these abnormal hemoglobins other than with normal hemoglobin will result in a hemolytic anemia. If the abnormal hemoglobin is heterozygous with normal hemoglobin, an asymptomatic and non-anemic trait will be present. These abnormal hemoglobins depend on a single Mendelian factor, and have been found in Negroes but not in whites.

The Hereditary Anenmias:

Hemoglobin C Disease: Although three observers have seen examples of homozygous hemoglobin C, the reports are not yet published. Our one case is characterized by mild anemia and 60-90% target cells in the peripheral blood. The patient has mild arthralgia and abdominal pain, but no crises. The spleen is not palpable. The exact mechanism that leads to the destruction of the red cells is not at all clear, other than the fact that target cells are apparently mechanically fragile. Why the abnormal hemoglobin is associated with target cell formation is another unanswered question.

Hemoglobin C-Sickle Cell Disease: The combination of hemoglobin C and S occurs in a ratio of 1: I and results in a mild hemolytic anemia with mild crises, splenomegaly and a great increase in target cells. The incidence of hemoglobin C, occurring as a heterozygous trait, or in combination with C or S, has been variously reported to occur in 0.5 % to 2%of American Negroes. About 30-40% of the hemoglobin of individuals heterozygous for this factor is electrophoretically abnormal.

Hemoglobin D Disease: Homozygous hemoglobin D has not yet been found, but its presence can be predicted. Only two instances of hemoglobin D trait (heterozygous) have so far been reported, and these were in two Caucasian siblings. Clinical and hematologic data have not yet been given.

Thalassemia-Sickle Cell Disease: The combination of the thalassemia gene with the sickle gene apparently favors penetrance of the sickling gene, since about 70% of the hemoglobin is S hemoglobin. About nineteen families have been studied where this combination was found.26 the clinical picture is similar to that of relatively mild sickle cell anemia, but the spleen is usually enlarged. Hematologically the anemia is hemolytic in type, but is microcytic and hypochromic with many target cells [9].

Nutritional Anemias

Nutritional anemia or anemia due to dietary causes is the most common form, yet, it is the easiest to manage compared to other forms of anemia. Some of the most common nutritional deficiencies are iron, cobalamin, folate, and also other elements like copper. Anemia due to diet is mostly asymptomatic in the initial phase until the stores are depleted, which can take a few months to several years, depending upon the cause [10].

Types of Nutritional Anemias:

Iron-Deficiency Anemia:

Iron deficiency anemia is a global health problem and common medical conditions seen in everyday clinical practice. Although the prevalence of iron-deficiency anemia has recently declined somewhat, iron deficiency continues to be the top-ranking cause of anemia worldwide and iron-deficiency anemia has a substantial effect on the lives of young children and premenopausal women in both low-income and developed countries. The diagnosis and treatment of this condition could clearly be improved.

Iron is crucial to biologic functions, including respiration, energy production, DNA synthesis, and cell proliferation.2 The human body has evolved to conserve iron in several ways, including the recycling of iron after the breakdown of red cells and the retention of iron in the absence of an excretion mechanism. However, since excess levels of iron can be toxic, its absorption is limited to 1 to 2 mg daily, and most of the iron needed daily (about 25 mg per day) is provided through recycling by macrophages that phagocytose senescent erythrocytes. The latter two mechanisms are controlled by the hormone hepcidin, which maintains total-body iron within normal ranges, avoiding both iron deficiency and excess.

Iron deficiency refers to the reduction of iron stores that precedes overt iron deficiency anemia or persists without progression. Iron-deficiency anemia is a more severe condition in which low levels of iron are associated with anemia and the presence of microcytic hypochromic red cells.

Iron-restricted erythropoiesis indicates that the delivery of iron to erythroid precursors is impaired, no matter how replete the stores. Stores may be normal or even increased because of iron sequestration in cases of anemia of chronic inflammation, which is observed in patients with autoimmune disorders, cancer, infections, and chronic kidney diseases. The presence of both iron deficiency and anemia of chronic disorders is common and may be seen in elderly patients5 and patients with chronic kidney disease. However, a substantial fraction of the anemia that is typical in elderly patients occurs in the absence of iron deficiency or elevated hepcidin levels.

Functional iron deficiency is a state of iron-poor erythropoiesis8 in which there is insufficient mobilization of iron from stores in the presence of increased demands, as is observed after treatment with erythropoiesis-stimulating agents.

Iron deficiency affects more than 2 billion people worldwide, and iron-deficiency anemia remains the top cause of anemia, as confirmed by the analysis of a large number of reports on the burden of disease in 187 countries between 1990 and 201014 and by a survey on the burden of anemia in persons at risk, such as preschool children and young women. Prevention programs have decreased rates of iron-deficiency anemia globally; the prevalence is now highest in Central and West Africa and South Asia. The estimated prevalence of iron deficiency worldwide is twice as high as that of iron-deficiency anemia.

The reported prevalence of iron deficiency in the absence of dietary fortification is approximately 40% in preschool children, 30% in menstruating girls and women, and 38% in pregnant women.These rates reflect the increased physiological need for dietary iron during specific life stages and according to sex. The growth spurt of adolescence is another critical period. For patients in any of these categories, pathologic causes of iron-deficiency anemia are often absent and extensive diagnostic workups are not advised. However, as discussed below, when the response to treatment is unsatisfactory, multiple causes should be considered, even in patients in these high-risk groups.

In developing countries, iron deficiency and iron-deficiency anemia typically result from insufficient dietary intake, loss of blood due to intestinal worm colonization, or both. In high income countries, certain eating habits (e.g., a vegetarian diet or no intake of red meat) and pathologic conditions (e.g., chronic blood loss or malabsorption) are the most common causes. Paradoxically, it appears to be more difficult to reduce the prevalence of iron-deficiency anemia in high-income countries than in lower-income countries. One reason for this seeming paradox is the high rate of iron deficiency in aging populations.

The mechanisms of iron acquisition are tightly regulated by hepcidin-based homeostatic controls. Hepcidin is a peptide hormone that is synthesized primarily in the liver. It functions as an acute-phase reactant that adjusts fluctuations in plasma iron levels caused by absorptive enterocytes and macrophages in the spleen by binding to and inducing the degradation of ferroportin, which exports iron from cells. Hepcidin expression increases in response to high circulating and tissue levels of iron and in persons with systemic inflammation or infection. Its production is inhibited by the expansion of erythropoiesis, iron deficiency, and tissue hypoxia in response to signals originating in the bone marrow, the liver, and probably muscle tissue and adipocytes.

Increases in hepcidin levels that are induced by inflammatory cytokines, especially interleukin-6, explain the iron sequestration and reduced supply of erythropoietic iron that occurs in the anemia of chronic disease. In the general population, hepcidin levels are low in girls and young women and higher — similar to levels in men — in postmenopausal women; fluctuations in hepcidin levels have a strong direct correlation with serum levels of ferritin. n iron deficiency, the transcription of hepcidin is suppressed. This adaptive mechanism facilitates the absorption of iron and the release of iron from body stores. Intestinal iron uptake from the gut lumen through divalent metal transporter 1 (DMT1) is increased by the activation of hypoxia-inducible factor

2α. The degree of store repletion determines the rapidity with which iron deficiency develops in cases of blood loss or a drastic reduction in iron absorption. Hepatocytes appear to be a long-term reservoir for iron and release it more slowly than macrophages.

Causes of iron deficiency anemia:

Poverty, malnutrition, and famine are self-explanatory causes of anemia in the multitude of people living with iron deficiency in developing countries, especially children and pregnant women. In addition, a cereal-based diet decreases iron bioavailability because phytates in grains sequester iron in a poorly absorbable complex. Other common causes in developing countries include hookworm infections and schistosomiasis, which cause chronic blood loss. Strict vegan and vegetarian diets, malabsorption, and chronic blood loss resulting from heavy menstrual osses are well-known causes of iron-deficiency anemia in developed countries. Chronic blood loss from the gastrointestinal tract, including occult blood, especially in male patients and elderly patients, may reveal the presence of benign lesions, angiodysplasia, or cancer. The origin of obscure gastrointestinal blood loss, especially from the small bowel, may be clarified by means of video-capsule endoscopy, which is increasingly used when conventional workups for iron-deficiency anemia return negative results.25 Persons who donate blood regularly are also at risk for iron deficiency, and their iron levels should be monitored.

In rare forms of intravascular hemolysis, iron is lost in the urine, and iron deficiency then aggravates anemia (e.g., in paroxysmal nocturnal hemoglobinuria). Anemia in endurance athletes may be due to hemolysis, blood loss, and often mild inflammation. Non-steroidal anti-inflammatory drugs and anticoagulants may contribute to blood loss, and proton-pump inhibitors are a frequently overlooked cause of impaired iron absorption.

The simultaneous occurrence of multiple causes of iron deficiency is common. In developing countries, low iron intake combined with intestinal infections with nematodes may result in severe anemia, especially in young children. The severity of iron deficiency is also associated with Ancylostoma duodenale (hookworm) load, according to the results of real-time polymerase chain-reaction assays of fecal samples.

In chronic schistosomiasis, blood losses combine with the anemia of inflammation. Patients with hypermenorrhea may also have concomitant malabsorption of iron. In end-stage kidney disease, iron-deficiency anemia results from blood loss during dialysis, reduced hepcidin clearance, inflammation, and certain drugs (e.g., proton-pump inhibitors and anticoagulants). In elderly persons, the prevalence of anemia correlates with advanced age and multiple related conditions, including iron deficiency, inflammatory disorders, decreased levels of erythropoietin, and cancer. Obesity may be associated with mild iron deficiency because of subclinical inflammation, increased hepcidin levels, and decreased iron absorption. Some studies report a high prevalence of iron deficiency (30 to 50%) in patients with congestive heart failure, probably because of

impaired iron absorption and inflammation: increased serum levels of hepcidin have been reported in the early stages of disease but not during disease progression.

Iron-deficiency anemia is usually acquired. However, the elucidation of systemic iron homeostasis has led to the recognition of a rare autosomal recessive disorder, iron-refractory iron-deficiency anemia (IRIDA) (Online Mendelian Inheritance in Man [OMIM] number, 206200). Iron-deficiency anemia is defined as "refractory" when there is an absence of hematologic response (an increase of <1 g of hemoglobin) after 4 to 6 weeks of treatment with oral iron. IRIDA is caused by a mutation in TMPRSS6, the gene encoding transmembrane protease, serine, also known as matriptase-2, which inhibits the signaling pathway that activates hepcidin. Loss-of-function mutations in TMPRSS6 reported in more than 50 families have led to constitutively high production of hepcidin, which blocks the intestinal absorption of iron. This type of anemia is variable, more severe in children, and unresponsive to treatment with oral iron. Typical findings include a striking microcytosis and extremely low transferrin saturation in the presence of normal or borderline-low ferritin levels and high hepcidin levels. The diagnosis ultimately requires sequencing of TMPRSS6. IRIDA represents less than 1% of the cases of iron-deficiency anemia seen in medical practice. However, knowledge of this condition is valuable to clinicians, since it clarifies how essential the suppression of hepcidin is to the body's response to pharmacologic iron. IRIDA also suggests the existence of genetic susceptibility to iron deficiency. Variants of TMPRSS6 have been associated with the modulation of serum hepcidin levels in individual persons, the variation in iron levels in population studies, and even with iron-deficiency anemia in elderly Chinese women. It is possible that coexisting acquired factors explain the ethnic specificity of the latter association.

In most cases, iron resistance is due to disorders of the gastrointestinal tract. Partial or total gastrectomy or any surgical procedure that bypasses the duodenum can cause resistance to oral iron. Bariatric surgery, such as laparoscopic Roux-en-Y gastric bypass, which is performed in selected obese patients to reduce caloric intake and to correct diabetes, is an emerging cause of iron deficiency and anemia because the procedure effectively removes an active iron absorption site from the digestive process and increases gastric pH. The limited follow-up data on patients who have undergone the procedure indicate that iron deficiency develops in up to 45%, particularly in women; lifelong nutritional monitoring and iron supplementation are advised. Helicobacter pylori infection decreases iron absorption, because the microorganism competes with its human host for available iron, reduces the bioavailability of vitamin C, and may lead to microerosions that cause bleeding. Since it is estimated that half the world's population is infected with H. pylori, clinicians should be aware of the possibility of infection and provide treatment in order to eradicate this source of iron-resistant iron-deficiency anemia. The prevalence of celiac disease and its atypical manifestations, which include iron-deficiency anemia, are increasingly recognized worldwide. In one study, screening for the prevalence of gluten sensitivity with the use of anti-transglutaminase antibodies uncovered negligible incidence among iron-replete participants, whereas 2.5% of participants with iron deficiency had

sensitivity to gluten. In another study of a series of patients with iron-refractory iron-deficiency anemia, 5% of participants had gluten sensitivity. These findings suggest that gluten sensitivity may be associated with iron refractory iron-deficiency anemia. Similarly, autoimmune atrophic gastritis, another rare cause of iron-refractory deficiency anemia, which results from an immune reaction against gastric parietal cells and intrinsic factor, should be considered as a possible albeit unlikely cause of iron-refractory microcytic anemia. In patients with inflammatory bowel disease, anemia may be iron-resistant, but it is multi-factorial, often resulting from a combination of deficiencies in iron, folate, and vitamin B_{12}, inflammation, and side effects from drug therapy.

Clinical Findings:

Iron-deficiency anemia is chronic and frequently asymptomatic and thus may often go undiagnosed. Weakness, fatigue, difficulty in concentrating, and poor work productivity are nonspecific symptoms ascribed to low delivery of oxygen to body tissues and decreased activity of iron-containing enzymes. The extent to which these nonhematologic effects of iron deficiency are manifested before anemia develops is unclear. Signs of iron deficiency in tissue are subtle and may not respond to iron therapy. Iron deficiency has been reported to decrease cognitive performance and to delay mental and motor development in children.

Severe iron-deficiency anemia in pregnancy is associated with an increased risk of preterm labor, low neonatal weight, and increased newborn and maternal mortality. Iron deficiency may predispose a person to infections, precipitate heart failure, and cause restless leg syndrome. In patients with heart failure, iron deficiency has a negative effect on the quality of life, irrespective of the presence of anemia.

Determination of Iron Status:

The traditional laboratory measures and results used to determine iron status and iron deficiency and related conditions (e.g., functional iron deficiency, iron-deficiency anemia, IRIDA, and anemia of chronic diseases) are well established. Serum ferritin level is the most sensitive and specific test used for the identification of iron deficiency (indicated by a level of <30 μg per liter). Levels are lower in patients with iron-deficiency anemia; a transferrin saturation level of less than 16% indicates an iron supply that is insufficient to support normal erythropoiesis. However, in determining iron status, it is important to consider the whole picture rather than relying on single test results. Guidelines for the differential diagnosis of microcytic anemias have recently been reviewed elsewhere. The diagnosis of iron-deficiency anemia in the context of inflammation is challenging and cannot be determined on the basis of the results of a single test .significantly higher cutoff levels for ferritin are used to define iron-deficiency anemia accompanied by inflammation, with the best predictor being a ferritin level of less than 100 μg per liter. Higher cutoff levels for ferritin are used in the diagnosis of iron deficiency in other conditions (e.g., <300 μg per liter for heart failure and for chronic kidney disease in the presence of a transferrin saturation level of less than 30%). The assessment of iron stores through iron

staining of bone marrow specimens obtained by means of biopsy is an option that is not used frequently.

Therapy:

Cautions and General Guidelines:

Patients with iron-deficiency anemia should receive iron supplementation. Caution must be used in areas in which malaria is endemic because supplementation may reverse the potentially protective effects of iron deficiency or increase the susceptibility to coinfections. In vitro studies have shown that the malaria parasite Plasmodium falciparum is less efficient in infecting iron-deficient erythrocytes than in infecting iron-replete erythrocytes, a protection that is reversed with iron supplementation. Some studies support the view that measurement of hepcidin levels could help to determine the best time (e.g., the end of malaria season) to provide children in these regions with iron supplementation. Emerging data suggest that non absorbed iron could be harmful to patients because it might modify the gut microbiota, increasing the concentration of intestinal pathogens.

The benefit of treating iron deficiency before the development of anemia remains uncertain. A few small studies show that the administration of intravenous iron improves fatigue in women without anemia whose ferritin levels are in the iron-deficient range. Some studies have also suggested that oral iron supplementation benefits physical performance in women of reproductive age, but such studies have included a limited number of participants and are strikingly heterogeneous.

Patients with severe iron-deficiency anemia that causes cardiovascular symptoms, such as heart failure or angina, should receive red-cell transfusions. This approach rapidly corrects not only hypoxia but also iron deficiency, since one unit of packed red cells provides approximately 200 mg of iron.

Oral Iron Therapy:

The administration of oral iron is a convenient, inexpensive, and effective means of treating stable patients. Among the myriad preparations on the market, iron sulfate is the most frequently used; gluconate and fumarate are also effective iron salts. The recommended daily dose for adults with iron deficiency is 100 to 200 mg of elementary iron and that for children is 3 to 6 mg per kilogram of body weight of a liquid preparation; for both groups the supplement should be administered in divided doses without food. The addition of vitamin C may improve absorption. The low hepcidin levels in patients with iron-deficiency anemia ensure effective iron absorption and the rapid recovery of hemoglobin levels; however, 3 to 6 months of treatment are required for the repletion of iron stores and the normalization of serum ferritin levels. Long-term use of oral iron is limited by side effects, including nausea, vomiting, constipation, and metallic taste; these side effects are frequent and, although not severe, are often worrisome to patients.

Although oral iron may cause dark stools, it does not produce false positive results on tests for occult blood. If treatment with oral iron fails, the reasons may include premature termination of treatment, lack of compliance with the regimen or discontinuation by the patient, or a truly refractory response to treatment. In the latter case, other, specific treatments, such as the eradication of infection with H. pylori or the introduction of a gluten-free diet in patients with celiac disease, may restore the capacity for iron absorption and eliminate the need for supplementation in some patients.29 There are no known markers that can be used to predict which patients will or will not have a response to oral iron therapy. The oral iron challenge test (in which 60 mg of oral iron is administered and serum iron levels are measured 1 to 2 hours afterward) is rarely used since it has not been extensively validated.

Preantral Iron Therapy:

The possibility of hypersensitivity reactions (including anaphylaxis) to high-molecular-weight iron dextran has traditionally limited the indications for the intravenous administration of iron. Newly approved, safer iron formulations are modifying this clinical practice (Table 3). Because the use of intravenous iron circumvents the problem of iron absorption, it is more effective and increases hemoglobin levels more quickly than oral iron. Another advantage is that in some patients the total dose required (up to 1000 mg) can be provided in a single infusion.

Patients with malabsorption and genetic IRIDA may require intravenous iron. Intravenous administration is also preferred when a rapid increase in hemoglobin level is required or when iron-deficiency anemia caused by chronic blood loss cannot be controlled with the use of oral iron, as is the case in patients with hereditary hemorrhagic telangiectasia. Active inflammatory bowel disease is an emerging indication for the use of intravenous iron; oral iron is not only ineffective but may also increase local inflammation. Intravenous iron is essential in the management of anemia in patients with chronic kidney disease who are receiving dialysis and treatment with erythropoiesis-stimulating agents. The addition of iron supplementation may eliminate or delay the need for these agents in some patients with chronic kidney disease who are not receiving dialysis. Erythropoiesis-stimulating agents are also used in selected patients with low-risk myelodysplastic syndrome and in patients with cancer who are receiving chemotherapy: in these circumstances, iron supplementation is usually limited to patients with concomitant iron deficiency or to those in whom there is no response to erythropoiesis-stimulating agents; intravenous iron is preferred when high hepcidin levels create a condition that is refractory to supplementation with oral iron. The way in which iron enhances the effect of erythropoiesis-stimulating agents is unclear. One hypothesis suggests that increased iron in macrophages leads to the over expression of ferroportin by means of the iron-responsive element–iron-regulatory protein system, which enhances the mobilization of iron for use in erythropoiesis. Intravenous iron should be avoided in the first trimester of pregnancy because of the lack of data on safety; it has an acceptable side-effect profile when used later in pregnancy.

Studies of the use of preantral iron therapy for conditions other than those mentioned are either limited or not controlled. A multicenter European trial of patients with iron deficiency and chronic heart failure showed that the use of intravenous iron supplementation led to improvements in physical performance, New York Heart Association functional class, and quality of life independently from the correction of anemia; more recently, 1 year of treatment was associated with a reduced risk of hospitalization. However, since these results were based largely on subjective evaluation, larger and longer-term studies are required to assess the real benefit of administering iron to patients with heart failure.

The transient side effects of intravenous iron supplementation include nausea, vomiting, pruritus, headache, and flushing; myalgia, arthralgia, and back and chest pain usually resolve within 48 hours, even after total dose administration. Hypersensitivity reactions are rare, as are severe or life-threatening reactions; the pathophysiological features of these reactions are uncertain and might be exacerbated by released free iron, a phenomenon that does not occur with currently used formulations. Predisposing conditions are rapid infusions, a history of atopy, and drug allergy. Practical recommendations for minimizing risk70 include a slow infusion rate, careful patient observation, and administration by trained health care personnel in an environment with access to resuscitation facilities. The test dose may provide false reassurance; premedication with antihistamine is no longer advised because it may cause hypotension and tachycardia.

Clinical trials are reassuring with regard to the efficacy and side-effect profile of intravenous iron. Some concern persists with regard to the long-term biologic effects of iron and its effects on the generation of oxygen radicals, patient susceptibility to infections, and the potential such treatment would have to worsen conditions such as type 2 diabetes and other chronic metabolic disorders. Well-designed, randomized, controlled trials are needed to verify the long-term effects of intravenous iron supplementation. In the interim, intravenous iron should be used only when the benefits outweigh the risks [11].

Folate-Deficiency Anemia:

Folate-deficiency anemia is the lack of folic acid in the blood. Folic acid is a B vitamin that helps your body make red blood cells. If you don't have enough red blood cells, you have anemia.

Red blood cells carry oxygen to all parts of your body. When you have anemia, your blood can't bring enough oxygen to all your tissues and organs. Without enough oxygen, your body can't work as well as it should.

Low levels of folic acid can cause megaloblastic anemia. With this condition, red blood cells are larger than normal. There are fewer of these cells. They are also oval-

shaped, not round. Sometimes these red blood cells don't live as long as normal red blood cells.

CAUSES:

It develops due to:

- You don't eat enough foods that have folic acid. These include green leafy vegetables, fresh fruits, fortified cereals, yeast, and meats (including liver).
- You drink too much alcohol.
- You have certain diseases of the lower digestive tract, such as celiac disease. This type of anemia also occurs in people with cancer.
- You take certain medicines, such as some used for seizures.
- Some babies are born unable to absorb folic acid. This can lead to megaloblastic anemia. With this condition, red blood cells are larger than normal. They also have a different shape. Early treatment is needed to prevent problems such as poor reasoning and learning.

Risk factors:
You are more likely to have this type of anemia if you:

- Don't eat a healthy diet
- Drink a lot of alcohol.
- Can't absorb folic acid
- Are taking certain medicines, such as those used to control seizures.
  Clinical features:

Symptoms may include:

- Pale skin
- Decreased appetite
- Being grouchy (irritable)
- Lack of energy or tiring easily
- Diarrhea
- Smooth and tender tongue.

The symptoms of folate-deficiency anemia may look like other blood conditions or health problems [12]..

Folate is required for the normal production of RBCs. Complications of a deficiency may include:

- Megaloblastic anemia, which means the RBCs are larger than normal and not fully developed.
- Low levels of white blood cells and platelets.
- Serious birth defects in the spinal cord and brain of a developing fetus, which are called neural tube defects.

  Treatment involves increasing the dietary intake of folate. You can also take a folate or folic acid supplement. Those with a genetic mutation that affects folate absorption, known as MTHFR, need to take methylated folate in order to avoid deficiency.

  Folate is frequently combined with other B vitamins in supplements. These are sometimes called vitamin B complexes. Pregnant women should completely avoid alcohol, and everyone else with a folate deficiency should decrease their alcohol intake [13].

Pediatric Anemia: diagnosis and treatment

Because anemia is common in children, doctors do routine screening for it. Plus, it often has no symptoms. Most anemias in children are diagnosed with these blood tests:

- **Hemoglobin and hematocrit:** This is often the first screening test for anemia in children. It measures the amount of hemoglobin and red blood cells in the blood.
- **Complete blood count (CBC):** A complete blood count checks the red and white blood cells, blood clotting cells (platelets), and sometimes, young red blood cells (reticulocytes). It includes hemoglobin and hematocrit and more details about the red blood cells.
- **Peripheral smear:** A small sample of blood is examined under a microscope to see if they look normal.

To get a blood sample, a healthcare provider will insert a needle into a vein, usually in the child's arm or hand. A tourniquet may be wrapped around the child's arm to help the healthcare provider find a vein. Blood is drawn up into a syringe or a test tube. In some cases, blood can be taken using a needle prick.

Blood tests may cause a little discomfort while the needle is inserted. It may cause some bruising or swelling. After the blood is removed, the healthcare provider will remove the tourniquet, put pressure on the area, and put on a bandage.

Depending on the results of the blood tests, your child may also have a bone marrow aspiration, biopsy, or both. This is done by taking a small amount of bone marrow fluid (aspiration) or solid bone marrow tissue (core biopsy). The fluid or tissue is examined for the number, size, and maturity of blood cells or abnormal cells.

Treatment:

Treatment will depend on your child’s symptoms, age, and general health. It will also depend on how severe the condition is.

The treatment for anemia depends on the cause. Some types do not require treatment. Some types may require medicine, blood transfusions, surgery, or stem cell transplants. Your child's healthcare provider may refer you to a hematologist. This is a specialist in treating blood disorders. Treatment may include:

- Vitamin and mineral drops or pills
- Changing your child's diet
- Stopping a medicine that causes anemia
- Medicine

- Surgery to remove the spleen
- Blood transfusions
- Stem cell transplants [14].

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